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(54) **Hydantoin derivatives, process for their preparation and pharmaceutical compositions containing the same as well as their use.**

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US-A- 3 384 643

CHEMICAL ABSTRACTS, vol. 95, no. 15, 12th October 1981, page 658, abstract-no. 132725m, Columbus, Ohio, US; M.A. EL-MAGHRABY et al.: "Synthesis of new heterocyclic sulfonamides"

(73) Proprietor: **MOCHIDA PHARMACEUTICAL CO., LTD.**
7, Yotsuya 1-chome
Shinjuku-ku Tokyo 160(JP)

(72) Inventor: **Mochida, Ei**
2-5-4, Komagome, Toshima-ku
Tokyo(JP)
Inventor: **Kato, Kazuo**
29-6, Fujimidai
Mishima-shi, Shizuoka-ken(JP)
Inventor: **Kato, Katsuaki**
779-25, Hagiwara
Gotenba-shi, Shizuoka-ken(JP)
Inventor: **Miwa, Ichitomo**
A-305 Miyukiyama-Park-Mansion 1201, Miyukiyama
Tenpaku-ku, Nagoya-shi, Aichi-ken(JP)
Inventor: **Okuda, Jun**
3-1110, Tsuchihara, Tenpaku-cho
Tenpaku-ku, Nagoya-shi, Aichi-ken(JP)

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CHEMICAL ABSTRACTS, vol. 97, no. 1, 5th July 1982, page 657, abstract-no. 6774e, Columbus, Ohio, US; A.M. EL-NAGGAR t al.: "Synthesis of thiophene-2-sulfonyl -amino acid and dipeptide derivatives"

(74) Representative: Hansen, Bernd, Dr.rer.nat. et al
Hoffmann, Eitle & Partner Patentanwälte Arabellastrasse 4 Postfach 81 04 20
W-8000 München 81(DE)

Description

BACKGROUND OF THE INVENTION

The present invention relates to novel hydantoin derivatives, processes for producing hydantoin derivatives, pharmaceutical compositions containing at least one of said hydantoin derivatives as aldose reductase inhibitors and novel intermediate compounds in the synthesis of said hydantoin derivatives.

Cataract, peripheral neuropathy, retinopathy and nephropathy associated with diabetes mellitus result from abnormal accumulation of polyol metabolites converted from sugars by aldose reductase. For example, sugar cataract results from damage of lens provoked by change in osmotic pressure induced by abnormal accumulation of polyol metabolites converted from glucose or galactose by aldose reductase in lens. Consequently, it is important to inhibit aldose reductase as strongly as possible for treating and/or preventing diabetic complications mentioned above. Although several compounds have been offered as aldose reductase inhibitors, none of them is fully sufficient in inhibitory activity against the enzyme. Therefore, it has been desired to develop new compounds having a stronger inhibitory activity against aldose reductase.

SUMMARY OF THE INVENTION

An object of the present invention is to provide novel hydantoin derivatives and salts, solvates and solvates of salts thereof.

Another object of the present invention is to provide processes for producing said novel hydantoin derivatives.

A further object of the present invention is to provide pharmaceutical compositions comprising at least one of said novel hydantoin derivatives having an inhibitory activity against aldose reductase.

A further object of the present invention is to provide novel intermediate compounds in the synthesis of said novel hydantoin derivatives.

The present inventors previously found that substituted phenylsulfonylhydantoin derivatives and naphthalenylsulfonylhydantoin derivatives had a strong inhibitory activity against aldose reductase and accomplished an invention on aldose reductase inhibitors. (JP-A-56 213518, 60 207113, 61 43770)

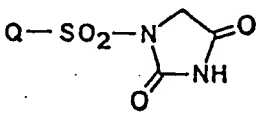
Furthermore, the present inventors have made extensive researches on a series of compounds having an inhibitory activity against aldose reductase and found novel hydantoin derivatives having an extremely strong inhibitory activity against aldose reductase. They are extremely useful for the treatment and/or prevention of various forms of diabetic complications based on the accumulation of polyol metabolites.

DETAILED DESCRIPTION OF THE INVENTION

As a result of extensive investigations concerning development of hydantoin derivatives having a satisfactory inhibitory activity against aldose reductase, the present inventors have found that novel hydantoin derivatives represented by the general formula (I) satisfy this requirement and have accomplished the present invention.

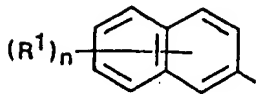
The present invention is based on the selection of a hydantoin which is bonded by a sulfonyl group to various substituents at the 1-position of the hydantoin skeleton.

The present invention is directed to novel hydantoin derivatives represented by the general formula (I):



(I)

and non-toxic salts, solvates and solvates of nontoxic salts thereof; wherein Q represents an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, a biphenylyl group, or a group:



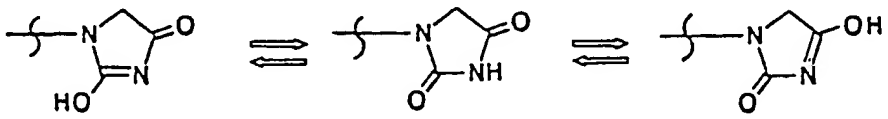
wherein R^1 represents an amino group which may be substituted with alkyl groups having 1 to 4 carbon atoms and/or acyl groups having 1 to 5 carbon atoms, a halogen atom, an alkyl group having 1 to 4 carbon atoms, an alkoxy group having 1 to 4 carbon atoms, a nitro group or a cyano group, or a combination of any of these groups when n represents an integer of 2 or more, and n represents an integer of 1, 2, 3 or 4, provided that when n represents an integer of 1, R^1 does not represent a bromine atom at 5-position of naphthalene ring.

The present invention is also directed to the process for preparing above-mentioned hydantoin derivatives.

The present invention is further directed to pharmaceutical compositions characterized by containing at least one of these hydantoin derivatives as active component(s).

The present invention is further directed to novel intermediate compounds in the synthesis of above-mentioned hydantoin derivatives.

In the hydantoin derivatives of the present invention represented by the general formula (I), it is known that the hydantoin moiety exhibits tautomerism as shown below:



Since these tautomeric isomers are generally deemed to be the same substance, the compounds of the present invention represented by the general formula (I) also include all of these tautomeric isomers.

The compounds represented by the general formula (I) may form salts with base. Typical examples of salts with base of the compounds represented by the general formula (I) include pharmaceutically acceptable salts such as alkali metal salts (such as sodium salts, potassium salts, etc.), alkaline earth metal salts (such as calcium salts, etc.), salts with organic bases (such as ammonium salts, benzylamine salts, diethylamine salts, etc.) or salts of amino acids (such as arginine salts, lysine salts, etc.). These salts of the compounds represented by the general formula (I) may be mono-salts or di-salts which may be salts of the hydantoin moiety and/or salts of the carboxy group contained in the Q group.

The compounds represented by the general formula (I) may also form acid addition salts. Typical example of acid addition salts of the compounds represented by the general formula (I) include pharmaceutically acceptable salts, such as salts of inorganic acids (such as hydrochlorides, hydrobromides, sulfates, phosphates, etc.), salts of organic acids (such as acetates, citrates, maleates, tartrates, benzoates, ascorbate, ethanesulfonates, toluenesulfonates, etc.) or salts of amino acids (such as aspartates, glutamates, etc.). These salts of the compounds represented by the general formula (I) may be salts of the heterocyclic moiety in the Q group.

In the compounds of the present invention represented by the general formula (I), the lower alkyl group can be defined more specifically as a straight or branched lower alkyl group having 1 to 4 carbon atoms such as methyl, ethyl, isopropyl, tert-butyl, etc. The alkoxy group can be defined more specifically as a straight or branched lower alkoxy group having 1 to 4 carbon atoms such as methoxy, ethoxy, isopropoxy, tert-butoxy, etc. The acyl group can be defined more specifically as a straight or branched lower acyl group having 1 to 5 carbon atoms such as formyl, acetyl, propanoyl, butanoyl, pivaloyl, etc.

The compounds of the present invention represented by the general formula (I) can be produced by the processes described as follows.

Namely;

The sulfonyl halide derivative represented by the general formula (II):

$$Q\text{-}SO_2\text{-}Y \quad (II)$$

wherein Q has the sam significance as defined above and Y represents a halogen atom, is reacted with a glycine derivative represented by th g neral formula (III):

$NH_2CH_2CO\text{-}R^2$ (III)

wherein R^2 represents a hydroxy group, an alkoxy group or an amino group which may b substituted with an alkoxycarbonyl group, to give the corresponding sulfonylglycine derivative represented by the general formula (IV):

$Q\text{-}SO_2NHCH_2CO\text{-}R^2$ (IV)

wherein Q and R^2 have the same significance as defined above. The condensation reaction is carried out generally in an aqueous solution, in an organic solvent (such as dichloromethane, chloroform, dioxane, tetrahydrofuran, acetonitrile, ethyl acetate, acetone, N,N-dimethylformamide, etc.) or in a mixed solvent of an aqueous solution and an organic solvent, preferably in the presence of deacidifying agent. As the deacidifying agent, triethylamine, diethylaniline, pyridine, etc. is employed in the organic solvent system, and in the aqueous system, aqueous alkali (such as sodium carbonate, sodium bicarbonate, potassium carbonate, sodium hydroxide, etc.) is employed. The condensation reaction is carried out at temperatures ranging from about -20 to 80 °C, preferably 0 °C to room temperature.

When R^2 represents an amino group in the general formula (IV), the sulfonylglycine derivative is represented by the general formula (IV'):

$Q\text{-}SO_2NHCH_2CONH_2$ (IV')

wherein Q has the same significance as defined above.

The sulfonylglycine derivative represented by the general formula (IV') is cyclized using a haloformic acid ester (such as methyl chloroformate, ethyl chloroformate, etc.) in the presence of a base (such as sodium hydride, potassium hydride, butyl lithium, etc.) to give the corresponding hydantoin derivative of the present invention represented by the general formula (I). The cyclization reaction is carried out generally in an inert solvent (such as N,N-dimethylformamide, dimethylsulfoxide, ethyl ether, tetrahydrofuran, dioxane, dichloromethane, etc.) and at temperatures ranging from about -20 to 120 °C, preferably 0 to 80 °C.

When R^2 represents a hydroxy group or an alkoxy group in the general formula (IV), the sulfonylglycine derivative is represented by the general formula (IV''):

$Q\text{-}SO_2NHCH_2CO\text{-}R^{2'}$ (IV'')

wherein Q has the same significance as defined above and $R^{2'}$ represents a hydroxy group or an alkoxy group.

The sulfonylglycine derivative represented by the general formula (IV'') is cyclized with a thiocyanate derivative (such as ammonium thiocyanate, potassium thiocyanate, etc.) in the presence of an acid anhydride (such as acetic anhydride, propionic anhydride, etc.) and, if necessary and desired, a base (such as pyridine, triethylamine, etc.) to give the corresponding 2-thiohydantoin derivative. If necessary and desired, the cyclization reaction is carried out after hydrolysis of ester when R^2 represents an alkoxy group. The cyclization reaction is carried out generally in an inert solvent (such as pyridine, triethylamine, N,N-dimethylformamide, dimethylsulfoxide, etc.) and at temperatures ranging from 0 to 120 °C, preferably room temperature to 100 °C. Further, the 2-thiohydantoin derivative obtained by said cyclization is oxidized using oxidizing agent (such as nitric acid, chlorine, iodine chloride, potassium permanganate, hydrogen peroxide, dimethylsulfoxide-sulfuric acid, etc.) to give the corresponding hydantoin derivatives of the present invention represented by the general formula (I).

To demonstrate the utility of the compounds of the present invention, experimental examples of representative compounds are shown below.

Compounds in the present invention

Compound 1:	1-(1-chloronaphthalen-2-ylsulfonyl)hydantoin
Compound 2:	1-(3-chloronaphthalen-2-ylsulfonyl)hydantoin
Compound 3:	1-(5-chloronaphthalen-2-ylsulfonyl)hydantoin
Compound 4:	1-(6-chloronaphthalen-2-ylsulfonyl)hydantoin
Compound 5:	1-(7-chloronaphthalen-2-ylsulfonyl)hydantoin
Compound 6:	1-(8-chloronaphthalen-2-ylsulfonyl)hydantoin

Compound 7: 1-(3,6-dichloronaphthalen-2-ylsulfonyl)hydantoin
Compound 8: 1-(1-bromonaphthalen-2-ylsulfonyl)hydantoin
Compound 9: 1-(3-bromonaphthalen-2-ylsulfonyl)hydantoin
Compound 10: 1-(6-bromonaphthalen-2-ylsulfonyl)hydantoin
Compound 11: 1-(5-nitronaphthalen-2-ylsulfonyl)hydantoin
Compound 12: 1-(3-methylnaphthalen-2-ylsulfonyl)hydantoin
Compound 13: 1-(6-methyl-5-nitronaphthalen-2-ylsulfonyl)hydantoin
Compound 14: 1-(7-methylnaphthalen-2-ylsulfonyl)hydantoin
Compound 15: 1-(6-methoxy-5-nitronaphthalen-2-ylsulfonyl)hydantoin

Reference compounds

Compound A: 1-(naphthalen-2-ylsulfonyl)hydantoin
Compound B: sorbinil

Experimental Example 1

The inhibitory activities of hydantoin derivatives on rat lens aldose reductase were measured according to the procedure of Inagaki et al. (K. Inagaki et al., Arch. Biochem. Biophys., 216, 337 (1982)) with slight modifications. Assays were performed in 0.1 M phosphate buffer (pH 6.2) containing 0.4 M ammonium sulfate, 10 mM DL-glyceraldehyde, 0.16 mM NADPH and aldose reductase (0.010-0.016 units) in a total volume of 1.0 ml. To this mixture was added 10 µl of the solution of each hydantoin derivative to be tested, and the decrease in absorbance at 340 nm was measured with a spectrophotometer.

The concentrations of typical hydantoin derivatives of the present invention required to produce 50% inhibition are shown in table 1.

Table 1

Compounds	IC_{50}(µmol/l)
1	0.29
2	0.16
3	0.19
4	0.14
5	0.39
6	0.46
7	0.24
8	0.094
9	0.35
10	0.17
11	0.10
12	0.14
13	0.027
14	0.35
15	0.038
A	0.66

Compounds 1 to 15 of the present invention showed stronger inhibitory activities against aldose reductase than reference compound A did. Above all, compound 13 and 15 were ten times or more potent than reference compound A.

Experimental Example 2

The inhibitory activities of hydantoin derivatives on bovine lens aldose reductase were measured according to the procedure of Inagaki et al. (K. Inagaki et al., Arch. Biochem. Biophys., 216, 337 (1982)) with slight modifications. Assay procedure was the same as described in Experimental example 1 except that bovine lens aldose reductase preparation was used instead of rat lens aldose reductase preparation.

The concentrations of the typical hydantoin derivatives of the present invention required to produce

50% inhibition are shown in table 2.

Table 2

Compounds	IC_{50} (μmol/l)
13	0.10
15	0.23
B	0.65

Compounds 13 and 15, of the present invention showed stronger inhibitory activities against aldose reductase than reference compound B did, which is a well known potent aldose reductase inhibitor.

Experimental Example 3

Hydantoin derivatives of the present invention were examined for acute toxicity. Groups of 5 ICR strain mice were orally administered with compound 7, 13, 14 or 15, of the present invention in a dose of 1 g/kg, and no change was observed in any of the eight groups over the one-week period after the administration.

Since the compounds of the present invention have strong inhibitory activities against aldose reductase and lower toxicity, pharmaceutical compositions containing at least one of these compounds as active component(s) are useful for the treatment and/or prevention of diabetic complications based on the accumlation of polyol metabolites.

The hydantoin derivatives provided by the present invention can be employed as pharmaceutical compositions, for example, in the form of pharmaceutical compositions containing hydantoin derivatives together with appropriate pharmaceutically acceptable carrier or medium such as sterilized water, edible oils, and non-toxic organic solvents. They may be mixed with excipients, binders, lubricants, coloring agents, corrigents, emulsifying agents or suspending agents to prepare tablets, powders, syrups, injections, eye drops, suppositories, ointments or inhalants. These agents can be administered either orally or parenterally and the amount of administration may be in the range of 1 to 3000 mg/day and may also be adjusted according to the patient conditions.

Hereafter the present invention will be described with references to the examples below but is not deemed to be limited thereof.

Example 1

Preparation of 1-(1-chloronaphthalen-2-ylsulfonyl)hydantoin (compound 1).

Step 1

Preparation of N-(1-chloronaphthalen-2-ylsulfonyl)glycine.

To a solution of potassium carbonate (21 g) and glycine (11 g) in water (300 ml) was added 1-chloronaphthalen-2-ylsulfonyl chloride (31 g) at room temperature, and the mixture was stirred under reflux for 30 minutes. After cooling to room temperature, the resultant solution was acidified with 2 N hydrochloric acid to a pH in the range of 1 to 2, and the formed precipitate was separated by filtration to give 33 g of the objective compound.

Melting point: 185.5 - 200.7 °C
IR (KBr, cm^{-1}): 3380, 1720, 1325, 1135
NMR (DMSO-d_6, ppm): 3.63 (2H, s), 7.59 - 8.51 (7H, m)

Step 2

Preparation of 1-(1-chloronaphthalen-2-ylsulfonyl)-2-thiohydantoin.

Anhydrous pyridine (19 ml), ammonium thiocyanate (17 g) and acetic anhydride (50 ml) were added to the product obtained in Step 1 (30 g), and the mixture was heated with stirring on a boiling water bath for 15 minutes. After cooling to room temperature, the resultant solution was poured into ice-water (300 ml), and the formed precipitate was separated by filtration to give 30.6 g of the objective compound.

Melting point: 268.6 °C (decomposition)
IR (KBr, cm^{-1}): 3150, 1790, 1765, 1380, 1190
NMR (DMSO-d_6, ppm): 4.93 (2H, s), 7.66 - 8.53 (5H, m), 8.78 (1H, s)

Step 3

Preparation of 1-(1-chloronaphthalen-2-ylsulfonyl)hydantoin.

A mixture of the product obtained in Step 2 (20 g) and 50% (w/v) nitric acid (100 ml) was heated with stirring on a boiling water bath for 40 minutes, and the resultant solution was cooled in an ice bath. The formed precipitate was separated by filtration and washed successively with water, ethyl alcohol, methyl alcohol and dichloromethane to give 4.8 g of the objective compound.
Melting point: 258.3 - 260.5 °C
IR (KBr, cm^{-1}): 3140, 1740, 1370, 1180
NMR (DMSO-d_6, ppm): 4.74 (2H, s), 7.80 - 8.39 (6H, m), 11.77 (1H, s)

Example 2

Preparation of 1-(1-bromonaphthalen-2-ylsulfonyl)hydantoin (compound 8).

Step 1

Preparation of N-(1-bromonaphthalen-2-ylsulfonyl)glycine.

Starting from 1-bromonaphthalen-2-ylsulfonyl chloride, the objective compound was obtained in a manner similar to Step 1 of Example 1.
Melting point: 199.7 - 204.1 °C
NMR (DMSO-d_6, ppm): 3.77 (2H, d, J = 6.0 Hz), 7.49 - 8.47 (7H, m)

Step 2

Preparation of 1-(1-bromonaphthalen-2-ylsulfonyl)-2-thiohydantoin.

Starting from the product obtained in Step 1, the objective compound was obtained in a manner similar to Step 2 of Example 1.
Melting point: 253.7 °C (decomposition)
NMR (DMSO-d_6, ppm): 5.01 (2H, s), 7.71 - 8.80 (6H, m)

Step 3

Preparation of 1-(1-bromonaphthalen-2-ylsulfonyl)hydantoin.

A mixture of the product obtained in Step 2 (7.5 g) and 50% (w/v) nitric acid (50 ml) was heated with stirring on a boiling water bath for 30 minutes and 60% (w/v) nitric acid (25 ml) was added. The reaction mixture was heated with stirring on a boiling water bath for 2 hours. The resultant solution was cooled in an ice bath, and the formed precipitate was separated by filtration and washed successively with water, methyl alcohol and dichloromethane to give 2.7 g of the objective compound.
Melting point: 287.4 - 292.5 °C
IR (KBr, cm^{-1}): 3200, 1740, 1370, 1180
NMR (DMSO-d_6, ppm): 4.78 (2H, s), 7.79 - 8.52 (6H, m), 11.75 (1H, s)

Example 3

Preparation of 1-(3,6-dichloronaphthalen-2-ylsulfonyl)hydantoin (compound 7).

Step 1

Preparation of N-(3,6-dichloronaphthalen-2-ylsulfonyl)glycine.

To a solution of potassium carbonate (11.7 g) and glycine (6.4 g) in water (140 ml) were added 3,6-dichloronaphthalen-2-ylsulfonyl chloride (20.8 g) and dioxane (50 ml) at room temperature, and the mixture was stirred under reflux for 2 hours. After cooling to room temperature, the resultant solution was acidified with 2 N hydrochloric acid to a pH in the range of 1 to 2, and extracted with ethyl acetate. The organic layer was washed with watery then with saturated aqueous NaCl solution, and dried over anhydrous sodium sulfate. Ethyl acetate was removed in vacuo to give 19.0 g of the objective compound.

Melting point: 185.0 - 188.2 °C
NMR (DMSO-d_6, ppm): 3.82 (2H, d, J = 8.0 Hz), 7.49 - 8.34 (5H, m), 8.63 (1H, s)

Step 2

Preparation of 1-(3,6-dichloronaphthalen-2-ylsulfonyl)-2-thiohydantoin

Starting from the product obtained in Step 1, the objective compound was obtained in a manner similar to Step 2 of Example 1.

Melting point: 252.8 °C (decomposition)
NMR (DMSO-d_6, ppm): 4.92 (2H, s), 7.38 - 8.32 (4H, m), 8.90 (1H, s)

Step 3

Preparation of 1-(3,6-dichloronaphthalen-2-ylsulfonyl)hydantoin.

Starting from the product obtained in Step 2, the objective compound was obtained in a manner similar to Step 3 of Example 1.

Melting point: 263.1 - 266.5 °C
IR (KBr, cm^{-1}): 3220, 1740, 1355, 1170
NMR (DMSO-d_6, ppm): 4.67 (2H, s), 7.74 (1H, d), 8.18 - 8.43 (3H, m), 8.98 (1H, s), 11.77 (1H, bs)

Example 4

Preparation of 1-(5-nitronaphthalen-2-ylsulfonyl)hydantoin (compound 11).

Step 1

Preparation of N-(5-nitronaphthalen-2-ylsulfonyl)glycine.

To a solution of potassium carbonate (3.2 g) and glycine (1.7 g) in water (50 ml) was added 5-nitronaphthalen-2-ylsulfonyl chloride (5 g) at room temperature, and the mixture was stirred under reflux for 5 minutes. After cooling to room temperature, the resultant solution was acidified with 2 N hydrochloric acid to a pH in the range of 1 to 2, and the formed precipitate was separated by filtration to give 5.4 g of the objective compound.

Melting point: 235.7 - 240.7 °C
IR (KBr, cm^{-1}): 3353, 1718, 1519, 1335, 1143
NMR (DMSO-d_6, ppm): 3.70 (2H, d, J = 5.9 Hz), 7.73 - 8.64 (7H, m), 12.60 (1H, bs)

Step 2

Preparation of 1-(5-nitronaphthalen-2-ylsulfonyl)-2-thiohydantoin.

Starting from the product obtained in Step 1, the objective compound was obtained in a manner similar to Step 2 of Example 1.

Melting point: 249.6 - 254.8 °C
IR (KBr, cm^{-1}): 3303, 1794, 1767, 1519, 1453, 1343, 1163
NMR (DMSO-d_6, ppm): 4.88 (2H, s), 7.80 - 9.03 (6H, m), 12.67 (1H, bs)

Step 3

Preparation of 1-(5-nitronaphthalen-2-ylsulfonyl)hydantoin.

Starting from the product obtained in Step 2, the objective compound was obtained in a manner similar to Step 3 of Example 1.

Melting point: 241.6 - 245.6 °C
IR (KBr, cm^{-1}): 3265, 1801, 1737, 1523, 1340 1170
NMR (DMSO-d_6, ppm): 4.58 (2H, s), 7.81 - 8.96 (6H, m), 11.64 (1H, bs)

Example 5

Preparation of 1-(6-acetamidonaphthalen-2-ylsulfonyl)hydantoin.

Step 1

Preparation of N-(6-acetamidonaphthalen-2-ylsulfonyl)glycine.

Starting from 6-acetamidonaphthalen-2-ylsulfonyl chloride, the objective compound was obtained in a manner similar to Step 1 of Example 1.

Melting point: 202.2 - 204.0 °C
NMR (DMSO-d_6, ppm): 2.11 (3H, s), 3.36 (2H, s), 5.01 (1H, bs), 7.58 - 8.40 (7H, m), 10.38 (1H, bs)

Step 2

Preparation of 1-(6-acetamidonaphthalen-2-ylsulfonyl)-2-thiohydantoin.

Starting from the product obtained in Step 1, the objective compound was obtained in a manner similar to Step 2 of Example 1.

Melting point: 274.0 - 276.9 °C
NMR (DMSO-d_6, ppm): 2.13 (3H, s), 4.85 (2H, s), 7.74 - 8.65 (6H, m), 10.30 (1H, s), 12.60 (1H, bs)

Step 3

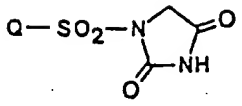
Preparation of 1-(6-acetamidonaphthalen-2-ylsulfonyl)hydantoin.

To a mixture of the product obtained in Step 2 (1.45 g), sodium bicarbonate (16 g), carbon tetrachloride (40 ml) and water (120 ml) was added slowly a solution of iodine monochloride (6.9 ml) in 1 N hydrochloric acid (40 ml) at room temperature. After stirring at room temperature for 10 minutes, 6 N hydrochloric acid (320 ml) was added, and the resultant solution was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium sulfite solution, then with saturated aqueous NaCl solution, and dried over anhydrous sodium sulfate. Ethyl acetate was removed in vacuo, and the residue was washed with dichloromethane to give 1.0 g of the objective compound.

Melting point: >300 °C
IR (KBr, cm^{-1}): 3400, 3250, 1740, 1360, 1165
NMR (DMSO-d_6, ppm): 2.14 (3H, s), 4.55 (2H, s), 7.60 - 8.56 (6H, m), 10.49 (1H, s), 11.60 (1H, s)

Compounds of Examples 6 to 25 prepared in a manner similar to Example 1 are summarized in the following table 3 together with corresponding IR and NMR data and melting points.

Table 3



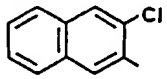
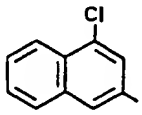
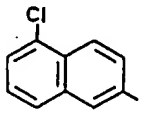
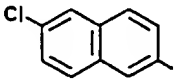
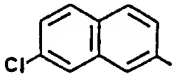
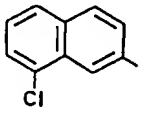
Ex. No.	Q	IR(KBr,cm^{-1})	NMR(DMSO-d$_6$,ppm)	M.P. (℃)
6		3250,1735, 1350,1160	4.57(2H,s), 7.67~8.34(5H,m), 8.74(1H,s), 11.60(1H,bs)	259.6 ~ 262.0
7		3250,1735, 1350,1165	4.58(2H,s), 7.89~8.73(6H,m), 11.62(1H,bs)	256.7 ~ 261.0
8		3230,1730, 1350,1160	4.57(2H,s), 7.62~8.80(6H,m), 11.62(1H,bs)	293.0 ~ 299.5
9		3230,1720, 1350,1150	4.57(2H,s), 7.69~8.75(6H,m), 11.61(1H,bs)	238.7 ~ 241.4
10		3160,1730, 1375,1170	4.56(2H,s), 7.71~8.70(6H,m), 11.62(1H,bs)	261.0 ~ 263.9
11		3230,1730, 1350,1160	4.56(2H,s), 7.69~8.82(6H,m), 11.61(1H,bs)	233.7 ~ 235.3

Table 3 (continued)

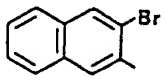
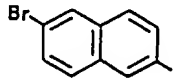
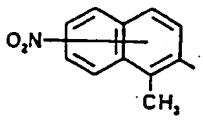
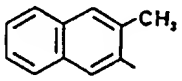
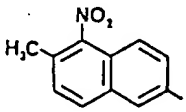
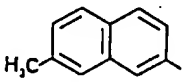
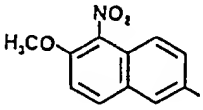
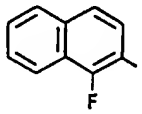
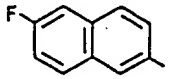
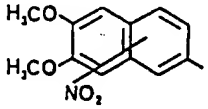
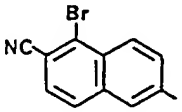
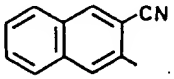
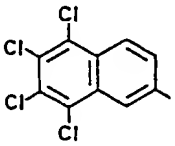
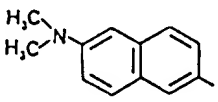
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
12		3240, 1730, 1360, 1180	4.72(2H, s), 7.74~8.26(4H, m), 8.54(1H, s), 8.96(1H, s), 11.77(1H, bs)	298.0 ~ 303.0
13		3220, 1730, 1350, 1160	4.57(2H, s), 7.80~8.74(6H, m), 11.61(1H, bs)	255.6 ~ 258.6
14		3250, 1735, 1520, 1340, 1150	3.08(3H, s), 4.58(2H, s), 7.90~8.73(5H, m), 11.69(1H, bs)	232.0 ~ 236.5
15		3200, 1725, 1340, 1160	2.70(3H, s), 4.55(2H, s), 7.62~8.14(5H, m), 8.75(1H, s), 11.65(1H, bs)	271.4 ~ 277.3
16		3170, 1730, 1530, 1370, 1170	2.52(3H, s), 4.55(2H, s), 7.74~8.48(4H, m), 8.85(1H, s), 11.62(1H, bs)	295.0 ~ 296.1
17		3240, 1735, 1350, 1160	2.53(3H, s), 4.56(2H, s), 7.51~8.63(6H, m), 11.58(1H, bs)	212.1 ~ 215.3
18		3180, 1740, 1530, 1370, 1170	4.11(3H, s), 4.54(2H, s), 7.75~8.83(5H, m), 11.61(1H, bs)	285.9 ~ 286.4

Table 3 (continued)

Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
19		3170, 1720, 1365, 1180	4.56(2H, s), 7.78~8.20(6H, m), 11.67(1H, bs)	231.0 ~ 234.0
20		3230, 1730, 1350, 1150	4.50(2H, s), 7.78~8.39(6H, m), 11.60(1H, bs)	162.6 ~ 166.0
21		3250, 1735, 1365, 1165	4.02(3H, s), 4.06(3H, s), 4.54(2H, s), 7.72~8.80(4H, m), 11.65(1H, bs)	228.0 ~ 230.0
22		3150, 2230, 1735, 1380, 1170	4.57(2H, s), 8.01~8.91(5H, m), 11.65(1H, bs)	279.0 ~ 285.0
23		3230, 2240, 1740, 1380, 1160	4.58(2H, s), 7.93~8.49(4H, m), 8.75(1H, s), 8.84(1H, s), 11.63(1H, bs)	261.6 ~ 264.6
24		3230, 1740, 1380, 1170	4.54(2H, s), 8.27~8.87(3H, m), 11.60(1H, bs)	>300
25		3240, 1740, 1370, 1170	2.94(6H, s), 4.53(2H, s), 7.35~8.59(6H, m), 11.56(1H, bs)	102.9 ~ 104.5

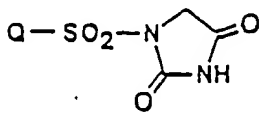
Compounds of Examples 26 to 28 were prepared starting from the corresponding sulfonyl chloride to obtain the sulfonyl glycine. From the latter the thiohydantoin was prepar d in a manner similar to step 2 of Example 1.

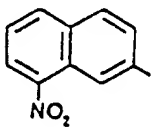
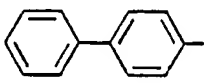
The hydantoin derivative was then obtained by adding to a suspension of iodine monochloride (7.12 ml) in 1N hydrochlorid acid (200 ml) successively the thiohydantoin. The mixture was stirred for 20 minutes at room temperature. After adding sodium bicarbonate (6.85 g), the reaction mixtures was stirred for 15

minutes and extracted twice with ethyl acetate (1 l + 300 ml). The organic layer was washed with saturated aqueous sodium bisulfite solution and then saturated with aqueous NaCl solution, and dried over anhydrous magnesium sulfate. Ethyl acetate was removed in vacuo, the residue was washed with dichloromethane to give the objective compound.

The corresponding IR and NMR data and melting points are summarized.

Table 4



Ex. No.	Q	IR(KBr,cm^{-1})	NMR(DMSO-d_6,ppm)	M.P. (℃)
26		1803,1755, 1516,1372, 1350,1165	4.55(2H,s), 7.86-9.10(6H,m), 11.62(1H,bs)	284.6 (dec.)
27	CH_3—	1744,1384, 1359,1164, 1153	3.35(3H,s), 4.33(2H,s), 11.65(1H,bs)	196.2 ~ 198.3
28		1749,1727, 1371,1170	4.55(2H,s), 7.38-8.16(9H,m), 11.63(1H,bs)	261.0 ~ 261.5

Compounds of Examples 29 and 30 were prepared as follows:

Step 1

Preparation of the corresponding glycine ethyl ester

To a suspension of the corresponding sulfonyl chloride and glycine ethyl ester hydrochloride in dichloromethane (320 ml) was added slowly triethylamine (3.03 ml) under ice-cooling, and the mixture was stirred for 160 minutes at room temperature. The stoichiometric ratio of the starting compounds was comparable to that of the previous examples. Water (200 ml) was added to the resultant solution and extracted with dichloromethane. The organic layer was washed successively with 1N hydrochloric acid, water and saturated aqueous NaCl solution, and dried over anhydrous magnesium sulfate. Dichloromethane was removed in vacuo, and the residue was reprecipitated from ethyl acetate and hexane to give the objective compound.

Step 2

Preparation of the corresponding glycine

A solution of sodium hydroxide (12.4 g) in water (73 ml) was added to a solution of the product obtained in Step 1 (41.4 g) in tetrahydrofuran (730 ml), and the mixture was stirred for 25 minutes at 60°C. After removing the solvent, water (300 ml) was added to the residue, and the resultant solution was acidified with concentrated hydrochloric acid to a pH of 1 under ice-cooling. The acidified solution was extracted thrice with ethyl acetate (800 ml), the organic layer was washed with water, then with saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. Ethyl acetate was removed in vacuo, the residue was reprecipitated from ethyl acetate and hexane to give the objective compound.

Step 3

Preparation of the corresponding thiohydantoin

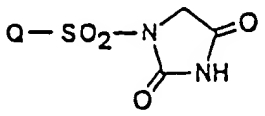
Starting from the product obtained in step 2, the objective compound was obtained in a manner similar to step 2 of Example 1.

Step 4

Preparation of the hydantoin derivative

Starting from the product obtained in step 3, the objective compound was obtained in a manner similar to step 3 of Example 1.
In the following Table 5 the corresponding IR and NMR data and melting points are summarized.

Table 5



Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (°C)
29		1721, 1367, 1349, 1172, 1161	0.96~2.40(10H, m), 3.30~3.69(1H, m), 4.31(2H, s), 11.61(1H, bs)	154.9 ~ 156.7
30		1735, 1725, 1359, 1163	0.69~1.98(15H, m), 3.42~3.59(2H, m), 4.33(2H, s), 11.64(1H, bs)	141.3 ~ 143.2

Intermediate compounds which lead to the above disclosed end product are summarized in th following Tables 6 and 7, together with the corresponding IR and NMR data and melting points.

Table 6

$Q-SO_2NHCH_2CO_2H$

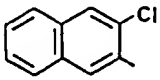
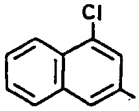
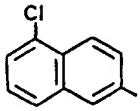
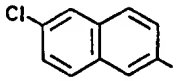
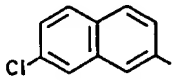
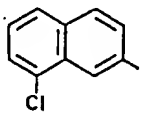
Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
6		3345, 1710, 1315, 1140	3.69 (2H, d), 7.61~8.37 (6H, m), 8.49 (1H, s)	174.5 ~ 182.1
7			3.70 (2H, d, J=5.9Hz), 7.72~8.50 (7H, m)	185.2 ~ 186.4
8			3.44 (2H, s), 7.52~8.60 (7H, m)	>300
9		3350, 1715, 1320, 1145	3.55 (2H, d, J=5.8Hz), 7.51~8.30 (6H, m), 8.48 (1H, s)	158.8 ~ 165.7
10			3.73 (2H, s), 7.51~8.53 (7H, m)	247.8 ~ 254.7
11			3.69 (2H, d, J=6.0Hz), 7.58~8.71 (7H, m)	157.8 ~ 162.1

Table 6 (continued)

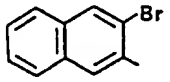
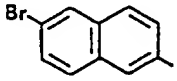
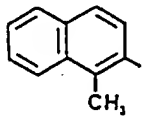
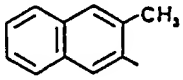
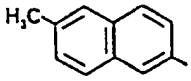
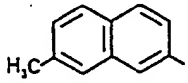
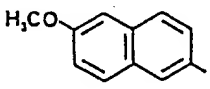
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
12		3345, 1715, 1330, 1165	3.78(2H, d, J=5.9Hz), 7.61~8.22(5H, m), 8.42(1H, s), 8.64(1H, s)	210.0 ~ 214.4
13		3350, 1715, 1320, 1145	3.48(2H, s), 7.52~8.48(7H, m)	257.2 ~ 265.7
14			2.98(3H, s), 3.62(2H, d, J=5.9Hz), 7.52~8.35(7H, m)	179.0 ~ 182.7
15			2.79(3H, s), 3.73(2H, d, J=6.1Hz), 7.43~8.35(6H, m), 8.53(1H, s)	155.5 ~ 160.5
16			2.49(3H, s), 3.40(2H, s), 7.35~8.39(7H, m)	225.7 ~ 230.6
17			2.49(3H, s), 3.65(2H, s), 7.35~8.45(7H, m)	147.4 ~ 152.0
18		3340, 1710, 1325, 1155	3.62(2H, d, J=6.0Hz), 3.91(3H, s), 7.19~8.15(6H, m), 8.31(1H, s)	161.4 ~ 163.6

Table 6 (continued)

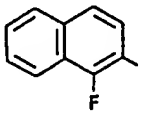
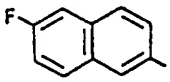
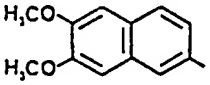
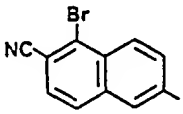
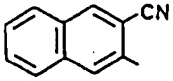
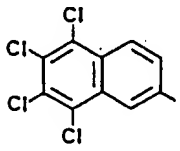
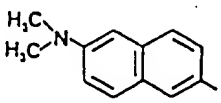
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
19			3.78(2H,d,J=5.9Hz), 7.67~8.45(7H,m)	163.5 ~ 168.5
20			3.62(2H,s), 7.05~8.50(7H,m)	109.0 ~ 109.5
21			3.55(2H,s), 3.93(6H,s), 7.35~7.98(5H,m), 8.24(1H,s)	212.6 ~ 217.1
22		3280, 2230, 1760, 1155	3.71(2H,d,J=6.0Hz), 7.87~8.65(6H,m)	231.9 ~ 234.9
23		3260, 2240, 1740, 1155	3.69(2H,d,J=6.0Hz), 7.82~8.73(7H,m)	186.2 ~ 192.0
24			3.72(2H,d,J=5.7Hz), 8.09~8.68(4H,m)	258.8 ~ 261.5
25			3.06(6H,s), 3.55(2H,d,J=6.0Hz), 6.91~8.21(7H,m)	148.0 ~ 152.0

Table 6 (continued)

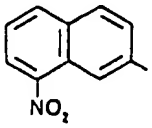
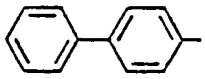
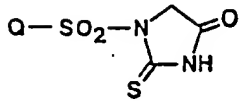
Ex. No.	Q	IR(KBr,cm^{-1})	NMR(DMSO-d$_6$,ppm)	M.P. (℃)
26		3348,1710, 1518,1334, 1142	3.68(2H,d,J=6.3Hz), 7.78-8.89(7H,m), 12.63(1H,bs)	224.9 - 227.7
27	CH_3—	3258,1711, 1320,1247, 1148	2.92(3H,s), 3.72(2H,d,J=5.9Hz), 7.39(1H,t,J=5.9Hz), 12.71(1H,bs)	168.0 - 171.0
28		3348,1714, 1323,1152	3.62(2H,d,J=6.3Hz), 7.44-7.87(9H,m), 8.06(1H,t,J=6.3Hz)	
29		3308,1714, 1319,1147, 1126	1.18-2.06(10H,m), 2.64-3.19(1H,m), 3.69(2H,d,J=6.0Hz), 7.33(1H,t,J=6.0Hz)	96.0 - 100.9
30		3314,3256, 2921,1716, 1313,1141	0.80-1.86(15H,m), 2.91-3.08(2H,m), 3.70(2H,d,J=5.9Hz), 7.39(1H,t,J=5.9Hz), 12.69(1H,bs)	

Table 7



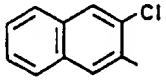
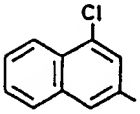
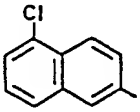
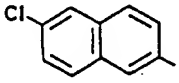
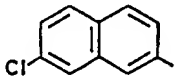
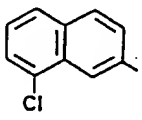
Ex. No.	Q	IR(KBr,cm^{-1})	NMR(DMSO-d$_6$,ppm)	M.P. (℃)
6		3130,1785, 1760,1165	4.90(2H,s), 7.69~8.45(5H,m), 8.88(1H,s)	212.9 ~ 222.8
7			4.88(2H,s), 7.74~8.83(6H,m)	250.1 (dec.)
8			4.89(2H,s), 7.59~8.43(5H,m), 8.70~8.96(1H,m)	231.4 (dec.)
9		3150,1795, 1770,1170	4.93(2H,s), 7.61~8.35(5H,m), 8.89(1H,s)	211.4 ~ 221.9
10			4.88(2H,s), 7.68~8.39(5H,m), 8.80(1H,s)	227.8 (dec.)
11			4.89(2H,s), 7.60~8.29(5H,m), 8.69~8.87(1H,m)	190.5 (dec.)

Table 7 (continued)

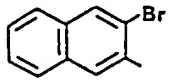
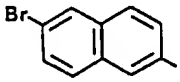
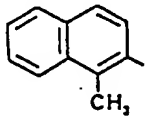
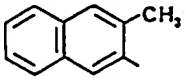
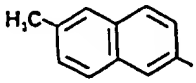
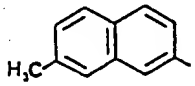
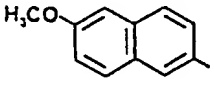
Ex. No.	Q	IR(KBr,cm^{-1})	NMR(DMSO-d_6,ppm)	M.P. (℃)
12		3270,1795, 1770,1170	4.94(2H,s), 7.65~8.51(5H,m), 8.99(1H,s)	248.5 ~ 255.7
13		3120,1785, 1755,1165	4.85(2H,s), 7.70~8.40(5H,m), 8.67~8.84(1H,m)	198.5 ~ 209.5
14			2.97(3H,s), 4.86(2H,s), 7.55~8.47(6H,m)	243.9 (dec.)
15			2.64(3H,s), 4.80(2H,s), 7.47~8.26(5H,m), 8.81(1H,s)	242.0 ~ 244.7
16			2.53(3H,s), 4.91(2H,s), 7.45~8.68(5H,m), 8.70(1H,s)	234.8 ~ 237.6
17			2.52(3H,s), 4.71(2H,s), 7.29~8.03(5H,m), 8.58~8.69(1H,m)	232.7 ~ 238.2
18		3250,1790, 1755,1165	3.94(3H,s), 4.85(2H,s), 7.23~7.51(2H,m), 7.87~8.17(3H,m), 8.67(1H,s)	236.4 (dec.)

Table 7 (continued)

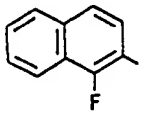
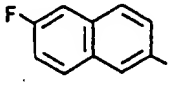
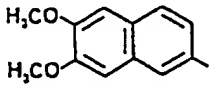
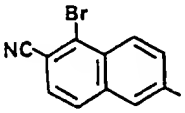
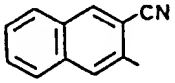
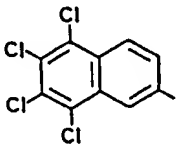
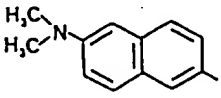
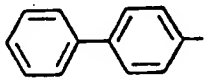
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
19			4.82(2H,s), 7.67~8.33(6H,m)	248.0 (dec.)
20			4.86(2H,s), 7.23~8.61(6H,m)	177.1 ~ 184.7
21			3.95(6H,s), 4.86(2H,s), 7.45~7.97(4H,m), 8.45~8.59(1H,m)	260.7 (dec.)
22		2230,1760, 1350,1170	4.88(2H,s), 7.88~8.55(4H,m), 8.73~9.00(1H,m)	223.0 (dec.)
23		2225,1760, 1350,1170	4.88(2H,s), 7.81~8.46(4H,m), 8.64~8.92(2H,m), 12.60(1H,bs)	131.0 ~ 135.8
24			4.86(2H,s), 8.46~8.99(3H,m), 12.60(1H,bs)	270.0 (dec.)
25			3.10(6H,s), 4.82(2H,s), 6.93~8.03(5H,m), 8.47(1H,s)	256.4 (dec.)

Table 7 (continued)

27	CH_3-	1745, 1470, 1424, 1361, 1165	3.57 (3H, s), 4.52 (2H, s), 12.70 (1H, bs)	213.4 ~ 216.0
28		1743, 1456, 1374, 1171	4.84 (2H, s), 7.47-8.23 (9H, m), 12.65 (1H, bs)	
29		1791, 1757, 1735, 1453, 1353, 1236, 1169	1.24-2.23 (10H, m), 3.90-4.32 (1H, m), 4.50 (2H, s), 12.70 (1H, bs)	
36		1748, 1735, 1454, 1363, 1235, 1157	0.54-2.04 (15H, m), 3.60-4.02 (2H, m), 4.51 (2H, s), 12.68 (1H, bs)	

Now, typical but non-limiting examples of formulations of the compound of this invention will be shown below.

Formulation A (Capsules)

Compound 13, 300 g of weight, 685 g of lactose and 15 g of magnesium stearate were weighed and mixed until the mixture became homogeneous. The mixture was then filled in No. 1 hard gelatin capsule at 200 mg each to obtain capsule preparation.

Formulation B (Tablets)

Compound 15, 300 g of weight, 550 g of lactose, 120 g of potato starch, 15 g of polyvinyl alcohol and 15 g of magnesium stearate were weighed. The weighed amount of compound 15, lactose and potato starch were mixed until accomplishing homogeneity. Then aqueous solution of polyvinylalcohol was added to the mixture and granulated by wet process. The granules were then dried, mixed with magnesium stearate and pressed into tablets, each weighing 200 mg.

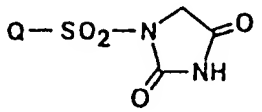
Formulation C (Powder)

Compound 8, 200 g of weight, 790 g of lactose and 10 g of magnesium stearate were weighed and mixed until the mixture became homogeneous to obtain 20% powder preparation.

Claims

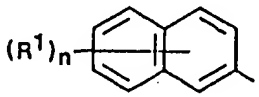
Claims for the following Contracting Stat s : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Hydantoin derivatives represented by th general formula (I):



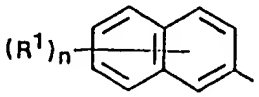
(I)

and non- toxic salts, solvates and solvates of non- toxic salts thereof; wherein Q represents an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, a biphenylyl group or a group:



wherein R^1 represents an amino group which may be substituted with alkyl groups having 1 to 4 carbon atoms and/or acyl groups having 1 to 5 carbon atoms, a halogen atom, an alkyl group having 1 to 4 carbon atoms, an alkoxy group having 1 to 4 carbon atoms, a nitro group or a cyano group, or a combination of any of these groups when n represents an integer of 2 or more, and n represents an integer of 1, 2, 3 or 4 , provided that when n represents an integer of 1, R^1 does not represent a bromine atom at 5-position of naphthalene ring.

2. Hydantoin derivatives as claimed in claim 1 wherein Q represents a group:



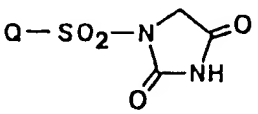
and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein R^1 and n have the same significance as defined above.

3. Hydantoin derivatives as claimed in claim 2 wherein n represents an integer of 1 and R^1 represents a halogen atom situated in 1-position of the naphthalene ring, and non-toxic salts, solvates and solvates of non-toxic salts thereof.

4. Hydantoin derivatives as claimed in claim 2 wherein n represents an integer of 1 and R^1 represents a halogen atom situated in 3-position of the naphthalene ring, and non-toxic salts, solvates and solvates of non-toxic salts thereof.

5. Hydantoin derivatives as claimed in claim 2 wherein n represents an integer of 1 and R^1 represents a nitro group situated in 5-position of the naphthalene ring, and non-toxic salts, solvates and solvates of non-toxic salts thereof.

6. A process for producing hydantoin derivatives represented by the general formula (I):



(I)

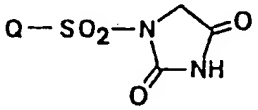
wherein Q has the same significance as defined in claim 1, by cyclization of the sulfonylglycine

derivative represented by the general formula (IV') :

$Q\text{-}SO_2NHCH_2CONH_2$ (IV')

wherein Q has the same significance as defined above, with a haloformic acid ester.

7. A process for producing hydantoin derivatives represented by the general formula (I):



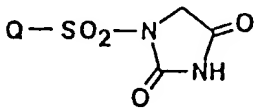
(I)

wherein Q has the same significance as defined in claim 1, by cyclization the sulfonylglycine derivative represented by the general formula (IV"):

$Q\text{-}SO_2NHCH_2CO\text{-}R^{2'}$ (IV")

wherein Q has the same significance as defined above, and $R^{2'}$ represents a hydroxy group or an alkoxy group, with a thiocyanate derivative, and then oxidizing the cyclized product.

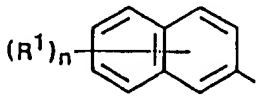
8. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a pharmaceutically effective amount of at least one of the hydantoin derivatives represented by the general formula (I):



(I)

and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein Q has the same significance as defined in claim 1.

9. A pharmaceutical composition as claimed in claim 8 wherein Q represents a group:



wherein R^1 and n have the same significance as defined above.

10. A pharmaceutical composition as claimed in claim 9 wherein n represents an integer of 1 and R^1 represents a halogen atom situated in 1-position of the naphthalene ring.

11. A pharmaceutical composition as claimed in claim 9 wherein n represents an integer of 1 and R^1 represents a halogen atom situated in 3-position of the naphthalene ring.

12. A pharmaceutical composition as claimed in claim 9 wherein n represents an integer of 1 and R^1 represents a nitro group situated in 5-position of the napthalene ring.

13. Intermediate compounds in the synthesis of hydantoin derivatives, said intermediate compounds being sulfonylglycine derivativ s represented by the general formula (IV):

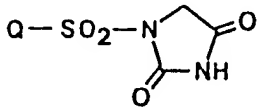
$Q\text{-}SO_2NHCH_2CO\text{-}R^2$ (IV)

wherein R^2 represents a hydroxy group, an alkoxy group or an amino group which may be substituted with an alkoxycarbonyl group, the alkoxy group having 1 to 4 carbon atoms, and Q has the same significanc as defined in compound (I) of claim 1.

14. The use of a compound according to claims 1 to 8 for the preparation of a pharmaceutical useful for the treatment of cataract or disorders of peripheral neuropathy, retinopathy and nephropathy.

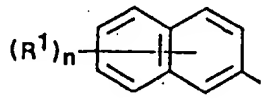
Claims for the following Contracting States : ES, GR

1. A process for producing hydantoin derivatives represented by the general formula (I):



(I)

and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein Q represents an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, a biphenylyl group or a group:



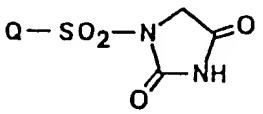
wherein R^1 represents an amino group which may be substituted with alkyl groups having 1 to 4 carbon atoms and/or acyl groups having 1 to 5 carbon atoms, a halogen atom, an alkyl group having 1 to 4 carbon atoms, an alkoxy group having 1 to 4 carbon atoms, a nitro group or a cyano group, or a combination of any of these groups when n represents an integer of 2 or more, and n represents an integer of 1, 2, 3 or 4, provided that when n represents an integer of 1, R^1 does not represent a bromine atom at 5-position of naphthalene ring,

by cyclization of the sulfonylglycine derivative represented by the general formula (IV') :

$Q\text{-}SO_2NHCH_2CONH_2$ (IV')

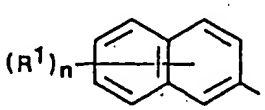
wherein Q has the same significance as defined above, with a haloformic acid ester.

2. A process for producing hydantoin derivatives represented by the general formula (I)



(I)

and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein Q represents an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms, a biphenylyl group or a group:



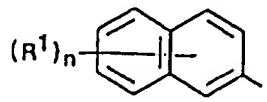
wherein R^1 represents an amino group which may be substituted with alkyl groups having 1 to 4 carbon atoms and/or acyl groups having 1 to 5 carbon atoms, a halogen atom, an alkyl group having 1 to 4 carbon atoms, an alkoxy group having 1 to 4 carbon atoms, a nitro group or a cyano group, or a combination of any of these groups when n represents an integer of 2 or more, and n represents an integer of 1, 2, 3 or 4, provided that when n represents an integer of 1, R^1 does not represent a bromine atom at 5-position of naphthalene ring,

by cyclization of the sulfonylglycine derivative represented by the general formula (IV''):

$$Q\text{-}SO_2NHCH_2CO\text{-}R^{2'} \quad (IV'')$$

wherein Q has the same significance as defined above, and $R^{2'}$ represents a hydroxy group or an alkoxy group, with a thiocyanate derivative, and then oxidizing the cyclized product.

3. The process according to claims 1 and 2, wherein Q represents the group



and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein R^1 and n have the same significance as defined above.

4. The process according to claim 3, wherein n represents an integer of 1 and R^1 represents a halogen atom situated in 1-position of the naphthalene ring, and non-toxic salts, solvates and solvates of non-toxic salts thereof.

5. The process according to claim 3, wherein n represents an integer of 1 and R^1 represents a halogen atom situated in 3-position of the naphthalene ring, and non-toxic salts, solvates and solvates of non-toxic salts thereof.

6. The process according to claim 3, wherein n represents an integer of 1 and R^1 represents a nitro group situated in 5-position of the naphthalene ring, and non-toxic salts, solvates and solvates of non-toxic salts thereof.

7. A process for the preparation of a pharmaceutical composition, characterized by formulating a pharmaceutically acceptable carrier and a pharmaceutically effective amount of at least one of the hydantoin derivatives as obtained by any of the processes of claims 1 to 6.

8. A process for the preparation of intermediate compounds useful in the synthesis of hydantoin derivatives according to claims 1 to 6, said intermediate compounds being sulfonylglycine derivatives represented by the general formula (IV):

$$Q\text{-}SO_2NHCH_2CO\text{-}R^2 \quad (IV)$$

wherein R^2 represents a hydroxy group, an alkoxy group or an amino group which may be substituted with an alkoxycarbonyl group, and Q has the same significance as defined in compound (I) of claim 1, characterized by reacting a sulfony halide derivative of formula (II)

$$Q\text{-}SO_2\text{-}Y \quad (II)$$

with a glycine derivative of formula (III)

$$NH_2CH_2CO\text{-}R^2 \quad (III)$$

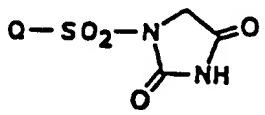
to give the corresponding compound (IV)

9. The use of a compound according to claims 1 to 8 for the preparation of a pharmaceutical useful for the treatment of cataract or disorders of peripheral neuropathy, retinopathy and nephropathy.

Revendications

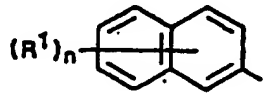
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Dérivés de l'hydantoïne représentés par la formule générale (I) :



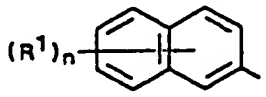
(I)

et leurs sels, solvates et solvates de sels non toxiques, Q représentant un groupe alkyle ayant 1 à 8 atomes de carbone, un groupe cycloalkyle ayant 3 à 6 atomes de carbone, un groupe biphénylyle, ou un groupe :



dans lequel R^1 représente un groupe amino qui peut être substitué par des groupes alkyle ayant 1 à 4 atomes de carbone et/ou des groupes acyle ayant 1 à 5 atomes de carbone, un atome d'halogène, un groupe alkyle ayant 1 à 4 atomes de carbone, un groupe alcoxy ayant 1 à 4 atomes de carbone, un groupe nitro ou un groupe cyano, ou une combinaison de n'importe lesquels de ces groupes lorsque n représente un entier égal à 2 ou davantage, et n représente un entier égal à 1, 2, 3 ou 4, sous réserve que, lorsque n représente un entier égal à 1, R^1 ne représente pas un atome de brome en position 5 du noyau naphtalène.

2. Dérivés de l'hydantoïne selon la revendication 1, dans lesquels Q représente un groupe :



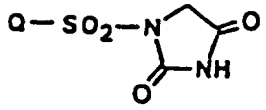
et leurs sels, solvates et solvates de sels non toxiques, où R^1 et n ont la même signification que celle qui correspond à la définition donnée ci-dessus.

3. Dérivés de l'hydantoïne selon la revendication 2, dans lesquels n est un entier égal à 1 et R^1 représente un atome d'halogène situé en position 1 du noyau naphtalène, et leurs sels, solvates et solvates de sels non toxiques.

4. Dérivés de l'hydantoïne selon la revendication 2, dans lesquels n représente un entier égal à 1 et R^1 représente un atome d'halogéne situé en position 3 du noyau naphtalène, et leurs sels, solvates et solvates de sels non toxiques.

5. Dérivés de l'hydantoïne selon la revendication 2, dans lesquels n est un entier égal à 1 et R^1 représente un groupe nitro situé n position 5 du noyau naphtalène, et leurs sels, solvates et solvates de sels non toxiques.

6. Procédé de préparation de dérivés de l'hydantoïne représentés par la formule générale (I) :



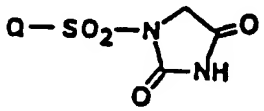
(I)

dans laquelle Q a la même signification que dans la revendication 1, par cyclisation du dérivé de sulfonylglycine représenté par la formule générale (IV'):

$Q\text{-}SO_2NHCH_2CONH_2$ (IV')

dans laquelle Q a la même signification que celle qui correspond à la définition donnée ci-dessus, avec un ester d'acide haloformique.

7. Procédé de préparation de dérivés de l'hydantoïne représentés par la formule générale (I) :



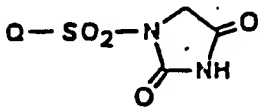
(I)

dans laquelle Q a la même signification que celle qui est définie dans la revendication 1, par cyclisation du dérivé de la sulfonylglycine représenté par la formule générale (IV"):

$Q\text{-}SO_2NHCH_2CO\text{-}R^{2'}$ (IV")

dans laquelle Q a la même signification que ci-dessus, et $R^{2'}$ représente un groupe hydroxy ou un groupe alcoxy, avec un thiocyanate, puis oxydation du produit cyclisé.

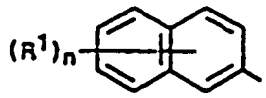
8. Composition pharmaceutique qui comprend un support pharmaceutiquement acceptable et une quantité pharmaceutiquement efficace d'au moins un des dérivés de l'hydantoïne représentés par la formule générale (I) :



(I)

et de leurs sels, solvates et solvates de sels non toxiques, Q ayant la même signification que dans la revendication 1.

9. Composition pharmaceutique selon la revendication 8, dans laquelle Q représente un groupe :



R^1 et n ayant la même signification que celle qui est définie ci-dessus.

10. Composition pharmaceutique selon la revendication 9, dans laquelle n représente un entier égal à 1 et R^1 représente un atome d'halogène situé en position 1 du noyau naphtalène.

11. Composition pharmaceutiqu selon la revendication 9, dans laquelle n représente un entier égal à 1 et

R^1 représente un atome d'halogène situé en position 3 du noyau naphtalène.

12. Composition pharmaceutique selon la revendication 9, dans laquelle n représente un ntier égal à 1 et R^1 représente un groupe nitro situé en position 5 du noyau naphtalèn .

13. Composés intermédiaires dans la synthèse des dérivés de l'hydantoïne, ces composés intermédiaires étant des dérivés de sulfonylglycine représentés par la formule générale (IV):

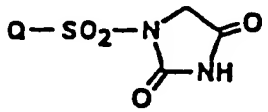
$$Q\text{-}SO_2NHCH_2CO\text{-}R^2 \quad (IV)$$

dans laquelle R^2 représente un groupe hydroxy, un groupe alcoxy ou un groupe amino qui peut être substitué par un groupe alcoxycarbonyle, le groupe alcoxy ayant 1 à 4 atomes de carbone, et Q a la même signification que dans le composé (I) de la revendication 1.

14. Utilisation d'un composé selon les revendications 1 à 8, pour la préparation d'un médicament utilisable pour le traitement de la cataracte ou de la neuropathie périphérique, de la rétinopathie et de la néphropathie.

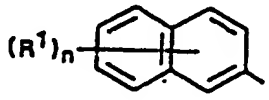
Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation de dérivés de l'hydantoïne représentés par la formule générale (I):



(I)

et leurs sels, solvates et solvates de sels non toxiques, Q représentant un groupe alkyle ayant 1 à 8 atomes de carbone, un groupe cycloalkyle ayant 3 à 6 atomes de carbone, un groupe biphénylyle ou un groupe :



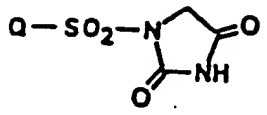
où R^1 représente un groupe amino qui peut être substitué par des groupes alkyle ayant 1 à 4 atomes de carbone et/ou des groupes acyle ayant 1 à 5 atomes de carbone, un atome d'halogène, un groupe alkyle ayant 1 à 4 atomes de carbone, un groupe alcoxy ayant 1 à 4 atomes de carbone, un groupe nitro ou un groupe cyano, ou une combinaison de n'importe lesquels de ces groupes, lorsque n représente un entier égal à 2 ou davantage, et n représente un entier égal à 1, 2, 3 ou 4, sous réserve que, lorsque n représente un entier égal à 1, R^1 ne représente pas un atome de brome en position 5 du noyau naphtalène,

par cyclisation du dérivé de la sulfonylglycine représenté par la formule générale (IV'):

$$Q\text{-}SO_2NHCH_2CONH_2 \quad (IV')$$

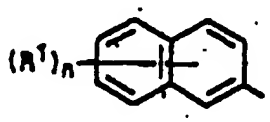
dans laquelle Q a la même signification que celle qui est définie ci-dessus, avec un ester d'acide haloformique.

2. Procédé de préparation de dérivés de l'hydantoïne représentés par la formule générale (I) :



(I)

et de leurs sels, solvates et solvates de sels non toxiques; dans laquelle Q représente un groupe alkyle ayant 1 à 8 atomes de carbone, un groupe cycloalkyle ayant 3 à 6 atomes de carbone, un groupe biphénylyle, ou un groupe :



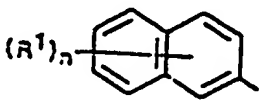
où R^1 représente un groupe amino qui peut être substitué par des groupes alkyle eayant 1 à 4 atomes de carbone et/ou des groupes acyle ayant 1 à 5 atomes de carbone, un atome d'halogène, un groupe alkyle ayant 1 à 4 atomes de carbone, un groupe alcoxy ayant 1 à 4 atomes de carbone, un groupe nitro ou un groupe cyano, ou une combinaison de n'importe lesquels de ces groupes lorsque n représente un entier égal à 2 ou davantage, et n représente un entier égal à 1, 2, 3 ou 4, sous réserve que lorsque n représente un entier égal à 1, R^1 ne représente pas un atome de brome en position position 5 du noyau naphtalène,

par cyclisation du dérivé de la sulfonylglycine représenté par la formule générale (IV"):

$Q\text{-}SO_2NHCH_2CO\text{-}R^{2'}$ (IV")

dans laquelle Q a la même signification que ci-dessus, et $R^{2'}$ représente un groupe hydroxy ou un groupe alcoxy, avec un thiocyanate, puis oxydation du produit cyclisé.

3. Procédé selon les revendications 1 et 2, dans lequel Q représente le groupe



et ses sels, solvates et solvates de sels non toxiques, où R^1 et n ont la signification indiquée ci-dessus.

4. Procédé selon la revendication 3, dans lequel n représente un entier égal à 1 et R^1 représente un atome d'halogène situé en position 1 du noyau naphtalène, et ses sels, solvates et solvates de sels non toxiques.

5. Procédé selon la revendication 3, dans lequel n représente un entier égal à 1 et R^1 représente un atome d'halogène situé en position 3 du noyau naphtalène, et ses sels, solvates et solvates de sels non toxiques.

6. Procédé selon la revendication 3, dans lequel n représente un entier égal à 1 et R^1 représente un groupe nitro situé en position 5 du noyau naphtalène, et ses sels, solvates et solvates de sels non toxiques.

7. Procédé pour la préparation d'une composition pharmaceutique, caractérisé en ce qu'on formule un support pharmaceutiquement acceptable et une quantité pharmaceutiquement efficace d'au moins un des dérivés de l'hydantoïne tel qu'obtenu par l'un quelconque des procédés selon les revendications 1 à 6.

8. Procédé pour la préparation de composés intermédiaires utilisables dans la synthèse des dérivés de

l'hydantoïne selon les revendications 1 à 6, ces composés intermédiaires étant des dérivés de sulfonylglycine, représentés par la formule générale (IV):

$Q\text{-}SO_2NHCH_2CO\text{-}R^2$ (IV)

dans laquelle R^2 représente un groupe hydroxy, un groupe alcoxy ou un groupe amino qui peut être substitué par un groupe alcoxycarbonyle, et Q a la même signification que pour le composé (I) de la revendication 1, caractérisé en ce qu'on fait réagir un dérivé d'halogénure de sulfonyle répondant à la formule (II):

$Q\text{-}SO_2\text{-}Y$ (II)

avec un dérivé de glycine répondant à la formule (III)

$NH_2CH_2CO\text{-}R^2$ (III)

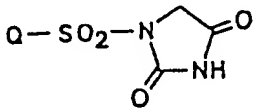
pour donner le composé (IV) correspondant.

9. Utilisation d'un composé selon les revendications 1 à 8, pour la préparation d'un médicament utile pour le traitement de la cataracte, ou de la neuropathie périphérique, de la rétinopathie et de la néphropathie.

Patentansprüche

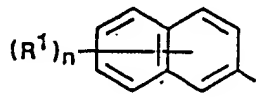
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Hydantoinderivate dargestellt durch die Formel (I):



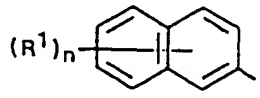
(I)

und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon, worin Q eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen, eine Cycloalkylgruppe mit 3 bis 6 Kohlenstoffatomen, eine Biphenylgruppe oder eine Gruppe darstellt:



worin R^1 eine Aminogruppe, die mit Alkylgruppen mit 1 bis 4 Kohlenstoffatomen und/oder Acylgruppen mit 1 bis 5 Kohlenstoffatomen substituiert sein kann, ein Halogenatom, eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen, eine Nitrogruppe oder ein Cyanogruppe oder ein Kombination dieser Gruppen darstellt wenn n 2 oder mehr ist, und n eine ganze Zahl von 1, 2, 3 oder 4 ist, vorausgesetzt daß, wenn n 1 ist, R^1 kein Bromatom an der 5-Position des Naphthalinringes darstellt.

2. Hydantoinderivate nach Anspruch 1, worin Q eine Gruppe darstellt



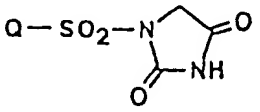
und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon, worin R^1 und n dieselben Bedeutung wie oben haben.

3. Hydantoinderivate nach Anspruch 2, worin n 1 ist und R^1 ein Halogenatom an der 1-Position des Naphthalinrings darstellt, und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon.

4. Hydantoinderivate nach Anspruch 2, worin n 1 ist, und R^1 ein Halogenatom an der 3-Position des Naphthalinrings darstellt und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon.

5. Hydantoinderivate nach Anspruch 2, worin n 1 ist, und R^1 eine Nitrogruppe an der 5-Position des Naphthalinrings darstellt, und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon.

6. Verfahren zur Herstellung von Hydantoinderivaten der Formel (I)



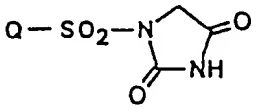
(I)

worin Q dieselbe Bedeutung wie in Anspruch 1 hat, durch Zyklisierung des Sulfonylglycinderivats der Formel (IV'):

$Q\text{-}SO_2NHCH_2CONH_2$ (IV')

worin Q dieselbe Bedeutung wie oben hat mit einem halogenierten Ameisesäureester.

7. Verfahren zur Herstellung von Hydantoinderivaten der Formel (I):



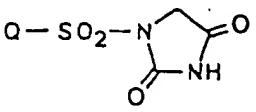
(I)

worin Q dieselbe Bedeutung wie in Anspruch 1 hat durch Zyklisierung des Sulfonylglycinderivats der Formel (IV''):

$Q\text{-}SO_2NHCH_2CO\text{-}R^{2'}$ (IV'')

worin Q dieselbe Bedeutung wie oben hat, und $R^{2'}$ eine Hydroxygruppe oder eine Alkoxygruppe darstellt, mit einem Thiocyanatderivat und anschließender Oxidation des zyklisierten Produkts.

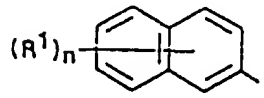
8. Pharmazeutische Zusammensetzung, die einen pharmazeutisch annehmbaren Träger und eine pharmazeutisch wirksame Menge von mindestens einem der Hydantoinderivate der Formel (I):



(I)

und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon, enthält, worin Q dieselbe Bedeutung wie in Anspruch 1 hat.

9. Pharmazeutische Zusammensetzung nach Anspruch 8, worin Q eine Gruppe darstellt:



worin R^1 und n dieselbe Bedeutung wie oben haben.

10. Pharmazeutische Zusammensetzung nach Anspruch 9, worin n 1 ist und R^1 ein Halogenatom an der 1-Position des Naphthalinrings darstellt.

11. Pharmazeutische Zusammensetzung nach Anspruch 9, worin n 1 ist und R^1 ein Halogenatom an der 3-Position des Naphthalinrings darstellt.

12. Pharmazeutische Zusammensetzung nach Anspruch 9, worin n 1 ist und R^1 eine Nitrogruppe an der 5-Position des Naphthalinrings darstellt.

13. Zwischenverbindungen bei der Synthese der Hydantoinderivate, wobei die Zwischenverbindungen Sulfonylglycinderivate der Formel (IV) darstellen

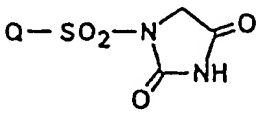
$Q\text{-}SO_2NHCH_2CO\text{-}R^2$ (IV)

worin R^2 eine Hydroxygruppe, eine Alkoxygruppe oder eine Aminogruppe darstellt, die mit einer Alkoxycarbonylgruppe substituiert sein kann, wobei die Alkoxygruppe 1 bis 4 Kohlenstoffe hat, und Q hat dieselbe Bedeutung wie in Verbindung (I) aus Anspruch 1.

14. Verwendung einer Verbindung nach den Ansprüchen 1 bis 8 zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung von grauem Star und/oder den Fehlfunktionen von peripherer Neuropathie, Retinopathie und Nephropathie.

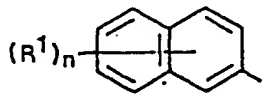
Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung von Hydantoinderivaten der Formel (I):



(I)

und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon, worin Q eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen, eine Cycloalkylgruppe mit 3 bis 6 Kohlenstoffatomen, eine Biphenylgruppe oder eine Gruppe darstellt:



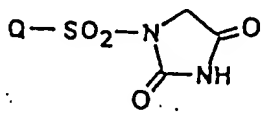
worin R^1 eine Aminogruppe, die mit Alkylgruppen mit 1 bis 4 Kohlenstoffatomen und/oder Acylgruppen mit 1 bis 5 Kohlenstoffatomen substituiert sein kann, in Halogenatom, eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Alkoxygrupp mit 1 bis 4 Kohlenstoffatomen, eine Nitrogruppe oder eine Cyanogruppe oder eine Kombination dieser Gruppen darstellt wenn n 2 oder mehr ist, und n eine ganze Zahl von 1, 2, 3 oder 4 ist, vorausgesetzt daß, wenn n 1 ist, R^1 kein Bromatom an der 5-Position des Naphthalinringes darstellt,

durch Zyklisierung des Sulfonylglycinderivats der Formel (IV'):

$Q\text{-}SO_2NHCH_2CONH_2$ (IV')

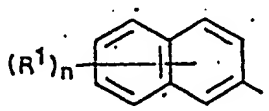
worin Q dieselbe Bedeutung wie oben hat mit einem halogenieren Ameisesäureester.

2. Verfahren zur Herstellung von Hydantoinderivaten der Formel (I):



(I)

und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon, worin Q eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen, eine Cycloalkylgruppe mit 3 bis 6 Kohlenstoffatomen, eine Biphenylgruppe oder eine Gruppe darstellt:

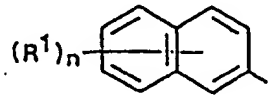


worin R^1 eine Aminogruppe, die mit Alkylgruppen mit 1 bis 4 Kohlenstoffatomen und/oder Acylgruppen mit 1 bis 5 Kohlenstoffatomen substituiert sein kann, ein Halogenatom, eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen, eine Alkoxygruppe mit 1 bis 4 Kohlenstoffatomen, eine Nitrogruppe oder eine Cyanogruppe oder eine Kombination dieser Gruppen darstellt wenn n 2 oder mehr ist, und n eine ganze Zahl von 1, 2, 3 oder 4 ist, vorausgesetzt daß, wenn n 1 ist, R^1 kein Bromatom an der 5-Position des Naphthalinringes darstellt,
durch Zyklisierung des Sulfonylglycinderivats der Formel (IV''):

$Q\text{-}SO_2NHCH_2CO\text{-}R^{2'}$ (IV'')

worin Q dieselbe Bedeutung wie oben hat und $R^{2'}$ eine Hydroxygruppe oder eine Alkoxygruppe darstellt, mit einem Thiocyanatderivat und anschließen-der Oxidation des zyklisierten Produkts.

3. Verfahren nach den Ansprüchen 1 und 2, worin Q die Gruppe darstellt



und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon, worin R^1 und n dieselbe Bedeutung wie oben haben.

4. Verfahren nach Anspruch 3, worin n 1 ist und R^1 ein Halogenatom an der 1-Position des Naphthalinrings darstellt, und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon.

5. Verfahren nach Anspruch 3, worin n 1 ist und R^1 ein Halogenatom an der 3-Position des Naphthalinrings darstellt, und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon.

6. Verfahren nach Anspruch 3, worin n 1 ist und R^1 eine Nitrogruppe in der 5-Position des Naphthalinrings darstellt, und nicht-toxische Salze, Solvate und Solvate von nicht-toxischen Salzen davon.

7. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung charakterisiert durch Formulie-

rung eines pharmazeutisch annehmbaren Trägers und einer pharmazeutisch wirksamen Menge von mindestens einem der nach einem der Verfahren der Ansprüche 1 bis 6 erhaltenen Hydantoinderivate.

8. Verfahr n zur Herstellung von Zwischenverbindungen zur Synthese der Hydantoinderivate nach Anspruch 1 bis 6, wobei die Zwischenverbindungen Sulfonylglycinderivate der Formel (IV) sind:

$Q\text{-}SO_2NHCH_2CO\text{-}R^2$ (IV)

worin R^2 eine Hydroxygruppe, eine Alkoxygruppe oder eine Aminogruppe darstellt, die mit einer Alkoxycarbonylgruppe substituiert sein kann, und Q hat dieselbe Bedeutung wie in Verbindung (I) aus Anspruch 1, **gekenzeichnet** durch Umsetzen eines Sulfonylhalogenidderivats der Formel (II)

$Q\text{-}SO_2\text{-}Y$ (II)

mit einem Glycinderivat der Formel (III)

$NH_2CH_2CO\text{-}R^2$ (III)

unter Erhalt der entsprechenden Formel (IV).

9. Verwendung einer Verbindung nach den Ansprüchen 1 bis 8 zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung von grauem Star oder Fehlfunktionen der peripheren Neuropathie, Retinopathie und Nephropathie.